Translation

PATENT COOPERATION TREATY

PCT

10/070,676

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference B0001WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FR00/02503	International filing date (*day/month/year*) 12 September 2000 (12.09.00)	Priority date (*day/month/year*) 13 September 1999 (13.09.99)
International Patent Classification (IPC) or national classification and IPC C12Q 1/68, C12N 15/11		
Applicant EXONHIT THERAPEUTICS SA		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30 March 2001 (30.03.01)	02 January 2002 (02.01.2002)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR00/02503

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 1-44, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-36, filed with the letter of 11 December 2001 (11.12.2001),
Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/fig 1-3, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

See supplemental Box.

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

See supplemental Box.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: II.

The claimed priority date of 13.09.1999 is recognized for the subject matter of Claims 1-16, 19-26, 28, 33, 34.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-29, 33, 34-36	**YES**
	Claims	30, 32	**NO**
Inventive step (IS)	Claims	1-29, 33, 34	**YES**
	Claims	30-32, 35, 36	**NO**
Industrial applicability (IA)	Claims	1-36	**YES**
	Claims		**NO**

2. Citations and explanations

Reference is made to the following documents:

D1: FR 2775984
D2: WO A 99 42606
D3: WO A 00 12760
D4: WO A 99 10529
D5: Proc. Natl. Acad. Sci., USA, Vol. 93, pp. 10614-10619, 10.1996

1. The subject matter of Claim 1 of the present application meets the requirements of novelty (PCT Article 33.2).

D1, published on 17.09.1999, and in the same scientific field, describes a method for evaluating the toxicity of a compound by using a library of nucleic acids specific to splicing events (Claims 34-36; page 28, line 21- page 29, line 26). D1 also describes using said method to identify agents connected to the phenomena of apoptosis or programmed cell death (Apoptotic pathways, page 26, line 18 - page 27, line 30) to identify antagonists or agonists of defined cell signal transduction pathways (p. 42, lines 13-15).

D1 does not describe the use of apoptosis genetic markers to evaluate the toxic potential of a compound on cells. Therefore, the technical features of the subject matter of Claim 1 can be considered to be novel [PCT Article 33(2)].

2. The subject matter of Claim 2 differs from the subject matter of Claim 1 by virtue of the use of marked probes corresponding to RNAs of non-treated cells and cells treated with toxic agents to identify diferentially expressed genes. The subject matter of Claim 2 can likewise be considered to be novel (PCT Article 33(2)].

3. Dependent Claims 3-23 describe specific applications of the methods of Claims 1 and 2. Said Claims 3-23 can likewise be considered to be novel [PCT Article 33(2)]. The subject matter of Claims 24-29 and 33,34 can likewise be considered to be novel for the same reason [PCT Article 33(2)].

4. The subject matter of Claims 1-29, 33, 34 is inventive [PCT Article 33(3)]. The present application describes that apoptosis markers can be used to determine the toxicity of a compound. The prior art cited does not suggest using nucleic acid libraries that are characteristic of apoptosis to evaluate the toxic potential of reference test compounds.

5. The subject matter of Claims 30-32 is not novel [PCT Article 33(2)]. Claims 30-32 describe specific sequences (Sequence ID 1-37) included in a nucleic acid kit or library. Moreover, Claims 30-32 are only characterized by the sequences seq ID 1-37. D2 describes genes of the Hox family that are expressed after a retinoic acid treatment (page 67, line 15 ff) and which can thus be used as toxicity markers. Document D5, in the microarrays field,

describes the use of cloned cDNA (i.e. HSP90) for detecting gene expression (see p. 10614, Column 1, paragraph 3, and Table 1). The HSP90 sequence is referred to as Sequence ID 29 in the present application. Consequently, said claims cannot be considered to be novel [PCT Article 33(2)]. The use of other genetic markers, which can be found using the method described in D2 and D5, is considered to entail the use of alternative genetic sequences which can be easily determined from D2. Consequently, the subject matter of Claims 30-32 cannot be considered to involve an inventive step [PCT Article 33(3)].

6. The subject matter of Claims 35 and 36 is not inventive [PCT Article 33(3)]. D4 describes a method for diagnosing SNP polymorphisms (see the claims and Example 3, page 17). A polymorphism in the LTC4 synthase gene is used to evaluate the response of a given compound. D4 also describes that a polymorphism of the gene affects the effectiveness of the same compound (page 7, lines 13-22). The method described in D4 identifies SNPs via a pharmacogenetic method. Therefore, identifying SNPs based on the modification of the response to a given compound cannot be considered to be inventive [PCT Article 33(3)].

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: VI.

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (validly claimed) (day/month/year)
WO 0012760	09.03.2000	27.08.1999	28.08.1998
			13.10.1998
			13.10.1998
FR A 2775984	17.09.1999	11.03.1998	

The subject matter of intermediate document D3 (WO 0012760) describes a method for evaluating the effect of toxic agents by using differentially expressed genetic markers (claims; page 6, line 10 ff., page 7, line 22). D3 is thus considered to describe the subject matter of Claims 30-32.

D1 (FR 2775984) is discussed in points 1 and 2.

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

1. Contrary to the requirement of PCT Rule 5.1(a)(ii), the relevant prior art disclosed in documents D1 and D2 has not been indicated in the description, nor have these documents been cited.

2. The patent description must be complete, i.e., it must be comprehensible on its own without having to refer to another document. In this respect, the paragraph on page 22, lines 25-29, "...included herein by way of reference" thus runs counter to the PCT Guidelines, Chapter II, 4.17.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. Claim 7 does not meet the requirements of PCT Article 6 because the expressions "isolated compound" and "mixture with other substances" are not defined.

2. Claim 18 does not meet the requirements of PCT Article 6 because it is not clear, even though the gene acronyms are known in the technical field.